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Revisión | Review

Medicinal plants used in Brazil Public Health System with neuroprotective potential – A systematic review

[Plantas medicinales utilizadas en el Sistema de Salud Pública de Brasil con potencial neuroprotector – Una revisión sistemática]

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Abstract: Current pharmacological therapies to treat neurological diseases are at best palliative and manage only the symptoms. Unfortunately, few therapies can affect diseases outcomes and alternative strategies such as stem cell therapy, neurotransplantation and deep brain stimulation are still in progress. Diseases such as Alzheimer's and Parkinson's disease become major public health challenge worldwide. In this way, the interest in the development of neuroprotective drugs of natural origin grows. Hence, this systematic review has quantified the studies that refer neuroprotective potential of plants listed in the Brazilian National List of Medicinal Plants of Interest to the Unified Health System (RENISUS). Searches were performed in two scientific databases (PubMed and Science Direct) from 2010 to 2016. A total of 4.532 articles met the inclusion criteria. 445 studies were considered eligible and were reviewed as full text. Following full analysis, 63 studies were included in this review. The studies covered 12 of the 71 plants belonging to RENISUS. In addition, two species are currently available in the Brazilian public health system as herbal medicine. This review may encourage and contribute to the proper use of medicinal plants in public health system.

Keywords: Neurodegenerative disease, neuroprotection, natural products, public health.

Resumen: Las terapias farmacológicas actuales para tratar enfermedades neurológicas son, en el mejor de los casos, paliativas y sólo controlan los síntomas. Desafortunadamente, pocas terapias pueden afectar los avances de las enfermedades y las estrategias alternativas tales como terapia con células madre, neurotransplantate y la estimulación profunda del cerebro están todavía en curso. Enfermedades como el Alzheimer y la enfermedad de Parkinson se convierten en un reto importante para la salud pública en todo el mundo. De esta manera, crece el interés en el desarrollo de fármacos neuroprotectores de origen natural. Por lo tanto, esta revisión sistemática ha cuantificado los estudios que hacen referencia al potencial neuroprotector de las plantas incluidas en la Lista Nacional Brasileña de Plantas Medicinales de Interés para el Sistema Único de Salud (RENISUS). Las búsquedas se realizaron en dos bases de datos científicas (PubMed y Science Direct) de 2010 a 2016. Un total de 4,532 artículos cumplieron los criterios de inclusión. 445 estudios se consideraron elegibles y se revisaron como texto completo. Después del análisis completo, se incluyeron 63 estudios en esta revisión. Los estudios abarcaron 12 de las 71 plantas pertenecientes a RENISUS. Además, actualmente hay dos especies disponibles en el sistema de salud pública brasileño como medicina herbaria. Esta revisión puede alentar y contribuir al uso adecuado de las plantas medicinales en el sistema de salud pública.

Palabras clave: Enfermedad neurodegenerativa, neuroprotección, productos naturales, salud pública.

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INTRODUCTION

As human life expectancy has increased, also has increased the incidence of neurodegenerative diseases such as Alzheimer's and Parkinson's. These neurodegenerative pathologies comprise a large variety of disorders that result in the loss of functional neurons and synapses (Solanki *et al.*, 2016). Unfortunately, neurological disorders are becoming major public health challenge worldwide and major cause of death (Rios *et al.*, 2016).

The use of vegetal extracts and phytochemicals for medicinal purposes such as prevention, treatment and cure of disorders is one of the oldest practices of traditional folk medicine (Lin, 2011; Huppert *et al.*, 2016). Despite the increased use of synthetic drugs in recent years, about 80% of the population in developing countries depend on medicinal plants as the only access to basic health care (Mendis *et al.*, 2007; Cordell & Colvard, 2012). Increasing evidences suggest that natural products are able to attenuate neurotoxicity. In addition, plant extracts may have a complementary or alternative role in preventing and/or treating neurodegenerative diseases (Lin, 2011; Pandareesh *et al.*, 2015). In view of that, the Brazilian public health system provides plant-derived phytomedicines to the population since 2007. In 2009, Brazil's Ministry of Health published the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) with the aim to encourage the use of complementary therapies in the Unified Health System (SUS), as well as to promote research on medicinal plants and to establish the correct and safe use of the same. It was prioritized the inclusion of native species of various biomes of the country. The plants were preselected by regions that alluded to its folk use. In addition, it was included plants whose effects have been scientifically proven. Currently, SUS offers the use of 12 herbal medicines (aloe, artichoke, cascara, cat's claw, devil's claw, espinheira-santa, guaco, mastic, mint, plantago, soy isoflavone and willow) derived from plants that belong to RENISUS (Marmitt *et al.*, 2016). Therefore, the aim of the present systematic review was to quantify the scientific reports on RENISUS plants with neuroprotective potential.

METHODS

Search strategy

We conducted a search in PubMed and ScienceDirect databases in an attempt to cover all studies investigated medicinal plants of RENISUS list that demonstrated neuroprotective potential. In this sense, we analyzed papers published since the creation of RENISUS in the period between January 2010 and December 2016. The keywords used to search were the scientific names of medicinal plants as described in RENISUS list.

Inclusion and exclusion criteria

In order to be considered in this analysis, articles had to meet the following two inclusion criteria: the neuroprotective potential of the medicinal plant; and evidence in preclinical or clinical phase. All scientific papers available as full and open access texts were considered, regardless of the language. Reviews, semi-structured interviews and research articles that addressed the chemical constituents of the plants without the intention to demonstrate neuroprotective potential were excluded. In addition, papers that only mentioned the empirical use of plants were also excluded.

Study selection

Two reviewers independently reviewed the retrieved articles and the analysis of these studies was performed in three steps. The primary search comprised the screening of titles and selecting those with terms related to neuroprotective potential. After reading the abstract of the previous chosen reports, irrelevant or duplicated papers were excluded. The final search consisted of full reading and qualitative analysis of the selected papers in order to elect those that mentioned some evidence of neuroprotective potential.

RESULTS

The database search retrieved 4.532 records. Out of a total of 1.289 pre-selected papers, 844 articles that did not meet the inclusion criteria were excluded and the remaining 445 articles were assessed for eligibility. Afterwards, 63 full text articles (1,39% of all searched papers) were considered suitable for this review. All selected reports were written in English and involved in vitro (21 studies), in vivo treatments (41 articles) and preclinical in humans (three research). Figure Nº 1 depicts an overview of the study selection procedure. The therapeutic effects attributed to the plants were analyzed according to Table Nº 1.

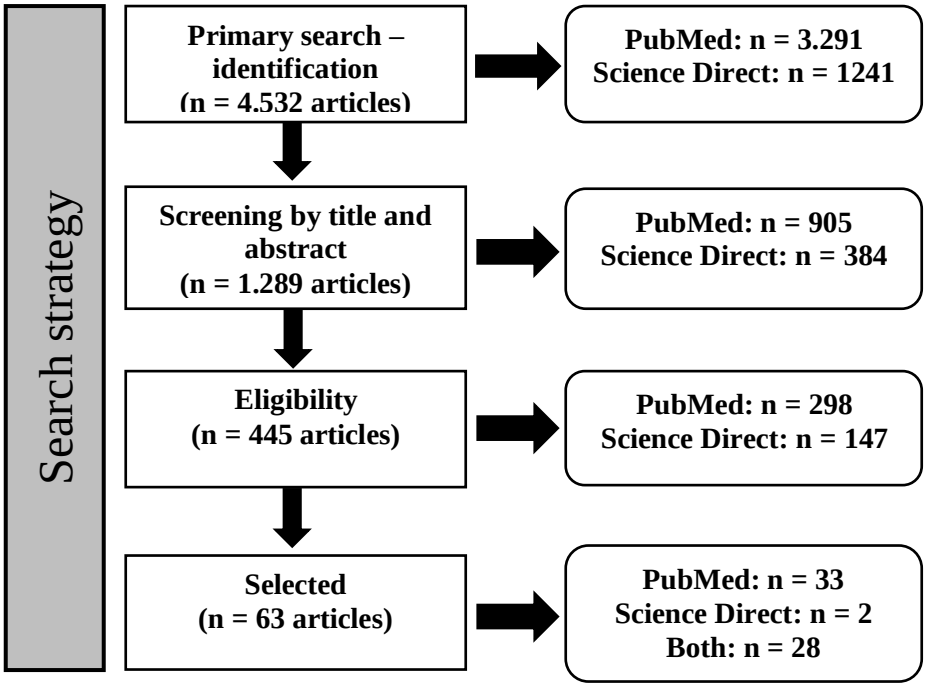

Figure Nº 1
Flowchart of the search strategy and study selection

Table Nº 1
Details on each study regarding methodological and outcome aspects of selected researches

Plant / family	Compound / plant part and concentration	Main results	Reference / country
Allium sativum L. (Amaryllidaceae)	Orally administered diallyl trisulfide (DATS) at 80 mg/kg body weight/day	DATS showed multifunctional neuroprotective effects in transgenic mice with amyotrophic lateral sclerosis (SOD1-G93A). Oral administration of the compound at the start of the clinical phase delayed the onset time of the disease. Treatment with the compound reduced the expression of the glial fibrillic acid protein (GFAP) and induced heme oxygenase-1 (HO-1) in the lumbar spinal cord of rats	Guo *et al*., 2011 China
Allium sativum L. (Amaryllidaceae)	Pretreated with S-Allylcysteine (SAC) (125 mg/kg intraperitoneal (i.p) daily for 17 days	SAC induced neuroprotective effect against oxidative stress induced by 1-Methyl-4-phenylpyridinium (MPP (+) model used to evaluate neuroprotective agents for Parkinson's disease) in the striatum of mice. In animals treated with SAC there was attenuation of MPP(+)-induced loss of striatal dopamine (DA) levels. The neuroprotective effect was associated with blockade of lipid peroxidation and reduction of superoxide radical production (positive regulation of Cu-Zn-superoxide dismutase activity). Behavioral analyses showed that SAC improved MPP(+)-induced impairment of locomotion	Rojas *et al*., 2011 Mexico
Allium sativum L. (Amaryllidaceae)	Allicin (1, 10 and 50 mg/kg) by i.p injection per day, respectively for 2	Allicin significantly reduced the volume of the spinal cord infarctions, improved the histopathologic features and increased the number of motor neurons in a dose-	Zhu *et al*., 2012 China

	weeks	dependent manner. Allicin also significantly suppressed the accumulations of protein and lipid peroxidation products, and increased the activities of endogenous antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione S-transferase (GST). Allicin exerts neuroprotection against spinal cord I/R injury in rabbits, which may be associated with the improvement of mitochondrial function.	
Allium sativum L. (Amaryllidaceae)	Garlic intake of the study population (2.9 g/day) in 125 Chinese patients with prior ischemic stroke (ISS)	Daily consumption of garlic protects endothelial function in patients with ischemic stroke and may play a role in the secondary prevention of atherosclerotic events through brachial artery flow-mediated dilatation (FMD). The daily ingestion of garlic correlated significantly with FMD	Lau *et al.,* 2013 China
Allium sativum L. (Amaryllidaceae)	Diallyl trisulfide (DATS) (10 µg/kg - 10 mg/kg)	DATS induced increase in p21Waf1 expression (cyclin-dependent p21 kinase inhibitor), which correlated with increased p53 expression and degradation of the MDM2 protein (p53 negative regulator). Compound reduced the tumor mass and the number of mitotic cells in the tumors. It decreased the activity of histone deacetylase (HDAC), pro-tumor markers (survivin, Bcl-2, c-Myc, mTOR, EGFR, VEGF), promoting apoptotic factors (Bax, mcalpian, caspase-3) in mice. DATS may be an effective therapeutic agent in preventing tumor progression and inducing apoptosis in human GBM in vivo without compromising liver function	Wallace *et al.,* 2013 USA
Allium sativum L. (Amaryllidaceae)	Animals were i.p treated with 50 mg/kg allicin and in vitro in culture of cortical neurons (50 µM)	The with allicin treatment in a model of mean occlusion of the cerebral artery of rats reduced the volume of the cerebral infarct, attenuated cerebral edema and decreased levels of neurological deficits. Allicin increased neuronal viability, decreased lactate dehydrogenase (LDH) release, and inhibited apoptotic neuronal death following oxygen deprivation. There was increased expression of sphingosine kinase 2 (Sphk2) both in vivo and in vitro	Lin *et al.,* 2015 China
Allium sativum L. (Amaryllidaceae)	Allicin (50 mg/kg i.p.) was administered 3 h after daily reperfusion in rats for five consecutive days	Allicin protects the brain from cerebral I/R injury induced by occlusion of middle cerebral artery occlusion (MCAO), which can be attributed to its anti-apoptotic and anti-inflammatory effects. Allicin reduced cerebral infarction area, brain water content, neuronal apoptosis, tumor necrosis factor-α (TNF-α) levels and myeloperoxidase (MPO) activity in the serum	Zhang *et al.,* 2015 China
Allium sativum L. (Amaryllidaceae)	Ethanol extract (0.5 or 1.0 %) and S-allylcysteine (SAC) (5 or 10 mM)	Extract and SAC, decreased cobalt chloride ($CoCl_2$) -induced hypoxia in PC-12 cells, derived from a pheochromocytoma of the rat adrenal medulla, a useful model for the study of nerve cell differentiation. Treatment with extract and SAC decreased reactive oxygen species (ROS) levels and the amount of cells in the early and late phases of apoptosis, this protective effect was associated with attenuation in stabilization of the subunit of the hypoxia-inducible factor	Orozco-Ibarra *et al.,* 2016 Mexico

		(HIF-1α)	
Calendula officinalis L. (Asteraceae)	Compounds 28-O-β-D-glucopyranosyl-oleanolic acid 3-O-β-D–glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS1) and oleanolic acid 3-O-β-D–glucopyranosyl (1→3)-β-D-glucopyranosiduronic acid (CS2) extracted from the butanol fraction of the seeds and tested in concentration (2.5, 5 and 10 µg/mL)	Compounds CS1 and CS2 exerted protection in mouse melanoma cells (B16), rat neuroblastoma (neuro-2A) line, against hydrogen peroxide (H_2O_2) induced toxicity. CS2 exhibited melanin biosynthesis stimulatory activity. CS1 showed a stimulatory effect for the production of hyaluronic acid in human dermal fibroblasts (NHDF-Ad). Both compounds did not show any inhibitory effect on both lipase and adipocyte differentiation. Compound CS2 can protect neuro-2A cells and increase cell viability against H_2O_2	Zaki *et al.,* 2016 Egypt, Japan and USA
Curcuma longa L. (Zingiberaceae)	A combination of candesartan 50 mg i.p and curcumin 60 mg/kg i.p 10 days before MCAO in mice	Curcumin combined with candersartan increases synergistically the inhibitory action of candesartan on cerebral ischemia in rats by suppressing changes in blood flow and oxidative stress via antioxidant properties, suggesting beneficial and preventive effects in ischemic brain damage. The treatment restored levels of SOD and glutathione-S-transferase (GST), thiobarbituric acid and heart rate	Awad, 2011 Egypt
Curcuma longa L. (Zingiberaceae)	Curcumin (5, 10, 15, 20 and 25 µM) for 24 h	Curcumin activates nuclear factor erythroid 2-related factor 2 (Nrf2) target genes in primary spinal cord astrocytes, decreases the level of intracellular ROS, and attenuates oxidative damage and mitochondrial dysfunction in vitro, which may serve as a therapeutic strategy for neurodegenerative diseases	Jiang *et al.,* 2011 China
Curcuma longa L. (Zingiberaceae)	Pretreated with curcumin (80 mg/kg body weight orally, in 1% w/v sodium carboxy methyl cellulose and 1% tween 80 in phosphate buffer saline) once daily for 3 weeks followed by a single injection of 6-OHDA in the striatum on the 22nd day	Parkinsonian model in rats induced by 6-hydroxydopamine (6-OHDA) (10 µg/2 µl in 0.1% ascorbic acid–saline) the behavioral activities were significantly preserved with curcumin pre-treatment (80 mg/kg for 21 days), attenuating levels of LPx, glutathione (GSH), GPX, glutathione reductase (GR), SOD, catalase (CAT) and tyrosine hydroxylase (TH). Curcumin is useful in preventing and has therapeutic potential in attenuation the Parkinson's disease	Khuwaja *et al.,* 2011 India
Curcuma longa L. (Zingiberaceae)	Curcumin (60 mg / kg) suspension orally (0.5% (w/v) sodium carboxymethylcellulose) daily for 14 days	Treatment with curcumin exerted a neuroprotective effect in the prevention of cortical dysfunction associated with diabetes in mice. The antioxidant potential of curcumin attenuated cholinergic dysfunction and oxidative stress and improved glucose transport and still delayed the associated diabetic complications. Treatment induced decreased gene expression of muscarinic M1, insulin receptor, SOD, choline acetyl transferase and increased	Peeyush Kumar *et al.,* 2011 India

		gene expression of muscarinic M3, α7-nicotinic acetylcholine receptor, acetylcholine esterase and glucose transporter 3 (GLUT3) in cerebral cortex of diabetic rats	
Curcuma longa L. (Zingiberaceae)	Curcumin (300 mg/kg, p.o.) dissolved in DMSO (50%) was administered orally by gavage at volumes not greater than 1.0 ml/100 g body weight	Co-administration of curcumin with four antiepileptic drugs (sodium valproate, phenytoin, phenobarbital and carbamazepine), acted as adjuvant in the epileptic seizure induced by pentylenetetrazol (PTZ) or induced by electroshock in mice. Co-administration increased effectiveness of treatments and reduced side effects. Co-administration of curcumin with sub-therapeutic dose of valproate significantly increased the latency to myoclonic jerks	Reeta *et al.,* 2011 India
Curcuma longa L. (Zingiberaceae)	Curcumin (IC50=24.9 μM)	Diet containing curcumin and co-treatment with cisplatin or doxorubicin increased cytotoxicity and apoptosis was observed in human neuroblastoma cells, SK-N-AS and SK-N-BE. Apoptosis was associated with decreased the nuclear factor-κB (NF-κB) activity and a reduction in the expression of Bcl-2 and Bcl-xL	Sukumari-Ramesh *et al.,* 2011 USA
Curcuma longa L. (Zingiberaceae)	Curcumin pretreatment intragastric (200 mg/kg) twice a day for 24 days	Curcumin pretreatment in rats the DA content reestablished in the striatum and the number of TH-immunoreactive neurons decreased after 6-OHDA treatment. The preventive and protective effects of curcumin against 6-OHDA may be attributable to the ironchelating activity of curcumin to suppress the iron-induced degeneration of nigral dopaminergic neurons	Du *et al.,* 2012 China
Curcuma longa L. (Zingiberaceae)	Curcumin (20 μM)	Combination of 20 μM curcumin and 10 nM paclitaxel (PTX) worked synergistically therapeutic action in human brain tumor stem cells (HBTSC) and human glioblastoma LN18 (p53 mutant and PTEN proficient) and U138MG (p53 mutant and PTEN mutant) cells, through induction of apoptosis, phosphorylation of Bcl-2 protein, cleavage of Bid to tBid, increase of Bax levels, mitochondrial release of cytochrome c, and apoptosis induction factor (AIF). Combination therapy inhibited cell proliferation, reduced the expression of survival factors and also angiogenic factors	Hossain *et al.,* 2012 USA
Curcuma longa L. (Zingiberaceae)	Curcumin (12.5, 2 and 50 mg/kg body weight) administred out once a day, 5 days each week, for 30 days	Exposure to cigarette smoke generated changes in the activity of acetylcholinesterase (AChE), influencing the loss of memory. Treatment with curcumin has been involved in the modulation of cholinergic neurotransmission, improved cognitive deficits induced by smoke, exerted a protective effect on learning and memory and decreases cholinergic alterations in rats exposed to smoke	Jaques *et al.,* 2012 Brazil
Curcuma longa L. (Zingiberaceae)	Oral administration of curcumin (30 mg/kg body weight) in drinking water	Supplementation of curcumin with 6-propyl-2-thiouracil (PTU) of 0,05% in rats for 30 days showed a significant reduction in the level of lipid peroxidation (LPx) in brain. The curcumin modulates the expression of superoxide dismutase in rat brain cortex and cerebellum under PTU-	Jena *et al.,* 2012a India

		induced hypothyroidism	
Curcuma longa L. (Zingiberaceae)	Oral administration of curcumin (30 mg/kg body weight) in drinking water	The decreased activity of superoxide dismutase (SOD) and protein expression of SOD1 in cerebellum of T4-treated rats were ameliorated after pretreatment administration of curcumin, which also induced a decrease in LPx levels. The regulation of expression of SOD by curcumin in different regions (cerebral cortex and cerebellum) of rat brain is different under hyperthyroidism	Jena *et al.,* 2012b India
Curcuma longa L. (Zingiberaceae)	Curcumin (50 mg/kg) was injected during 10 days (i.p.)	Curcumin exhibited neuroprotective effect against toxicity exerted by the intracerebroventricular administration of homocysteine, and consequently improved locomotor function in animals and preventing the onset of Parkinson's disease	Mansouri *et al.,* 2012 Iran
Curcuma longa L. (Zingiberaceae)	Bisabolene sesquiterpenoids extracted of dried rhizome powder	Bisabolene sesquiterpenoids exhibited anticonvulsant activities in a PTZ -induced seizure assay in larval zebrafish and rats showing possible neuromodulatory activity	Orellana-Paucar *et al.,* 2012 Belgium
Curcuma longa L. (Zingiberaceae)	Curcumin (20 µmol/L)	Curcumin protects against staurosporine (STS)-induced cytotoxicity in rat hippocampal neurons in primary culture assay in vitro. Caspase-3, heat shock protein 70, Akt and reactive oxygen species (ROS) activation may be involved in this protection	Qin *et al.,* 2012 China
Curcuma longa L. (Zingiberaceae)	Curcumin C3 Complex® per day in two divided doses for 24 weeks (2 gm or 4 gm)	Oral administration of C3 Complex® was associated with reduction of hematocrit and increase of glucose levels in a group of 36 patients with Alzheimer's disease, with good tolerance and limited bioavailability to compound	Ringman *et al.,* 2012 USA
Curcuma longa L. (Zingiberaceae)	Curcumin (100 mg/kg, orally) daily for 28 days	Curcumin protected against biochemical changes and oxidative damage induced by cypermethrin (CYP) in rats. Curcumin treatment decreased levels of biochemical markers and lipid peroxidation in the blood and increased levels of GSH, CAT and GPX, preserving the normal histological architecture of the liver, kidney and brain	Sankar *et al.,* 2012 India
Curcuma longa L. (Zingiberaceae)	Curcumin (30 and 60 mg/kg; oral gavage)	Treatment with curcumin showed protective effect and reversed cognitive déficits associated with increased AChE activity, neuroinflammation (oxidative-nitrosative stress, TNF-α, interleukins-1β (IL-1β) and TGF-β1) and neuronal apoptosis (NF-κB and caspase 3) in the cerebral cortex and hippocampus of mice pups postnatally exposed to etanol	Tiwari y Chopra, 2012 India
Curcuma longa L. (Zingiberaceae)	Tetrahydrocurcumin (THC) (25mg/kg/day 0.1% DMSO dose) was given for 3 days by i.p injection in mice after 30 min of ischemia induction	THC decreased oxidative damage and ameliorated the homocysteinylation of cyto-c in-part by metalloproteinase-9 (MMP-9) activation which leads to autophagy in I/R groups as compared to sham operated groups. This study suggests a potential therapeutic role of dietary THC in cerebral ischemia. The size of edema and cerebral infarction was reduced in animals treated with THC	Tyagi *et al.,* 2012 USA
Curcuma longa L. (Zingiberaceae)	Ten days after glioma implantation (C6), animals were trated with	Curcumin is a potential agent against the human (U138MG, U87 and U373) malignant glioblastomas (GBM) cell lines and glioma implantation (C6) in rat. In vitro, curcumin	Zanotto-Filho *et al.,* 2012 Brazil

	(50 mg/kg/day curcumin solubilized in sterile DMSO) were administered intraperitoneal (i.p) for 10 days	inhibited proliferation, migration and induced cell death in GBM growth models. In U138MG, curcumin decreased the constitutive activation of PI3K/Akt and the NF-κB pathway, inducing mitochondrial dysfunction as a prelude to apoptosis. In mice implanted with C6, curcumin decreased the volume of brain tumors by 81.8%. No tissue evidence of metabolic transaminases (creatinine and alkaline phosphatase) (cholesterol and glucose), oxidative damage or toxicity was observed	
Curcuma longa L. (Zingiberaceae)	Curcumin (50, 100, or 200 mg/kg) i.p. injection	Curcumin exhibited antidepressant effect through neurotrophic activity and increased brain-derived neurotrophic factor (BDNF) (antidepressant) in rat hippocampus. There was a dose-dependent reduction of immobility in the forced swim test (FST)	Hurley *et al.*, 2013 USA
Curcuma longa L. (Zingiberaceae)	Curcumin (1 μM)	Curcumin selectively inhibited L-type Ca^{2+} channels in cell cultures of rat hippocampal neurons. Reversibly inhibited high voltage-gated Ca^{2+} channel (HVGCC) currents (IBa) induced by the intracellular application of the PKC-θ peptide inhibitor or by the PKC-θ knockdown siRNA in rat hippocampal neurons. In these neurons, new PKC isoforms including PKC-δ, PKC-ε and PKC-θ were endogenously expressed. Compound inhibited the PKC-θ dependent IBavia pathway, which could contribute to its neuroprotective effects on rat hippocampal neurons	Liu *et al.*, 2013 China
Curcuma longa L. (Zingiberaceae)	Combination extract of four plants traditional chinese medicine, including rhizoma C. longa at concentrations (0.075 g/kg-1 x day-1, 0.15 g/kg-1 x day-1, 0.30 g/kg-1 x day-1) for 4 or 8 months	The combination of extracts containing *C. longa* rhizomes showed a neuroprotective mechanism in the prediction of Alzheimer's disease through inhibition of protein expression and also in immunohistochemical analysis of the 3β glycogen synthase-kinase (A-GSK-3β) target in the cerebral cortex of transgenic mice (APPV7171)	Shi *et al.*, 2013 China
Curcuma longa L. (Zingiberaceae)	Curcumin (2,5 μM and 5 μM) for 24 e 48 h	Neprilysin (NEP) is a poorly expressed metallopeptidase in the brain. Treatment with curcumin induced NEP gene restoration by demethylation of the CpG dinucleotide, concomitant with Akt inhibition, NF-κB suppression, and proinflammatory cytokines, cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS) in rat neuroblastoma cells (N2a), which suggests potential for treatment of Alzheimer's disease	Deng *et al.*, 2014 China
Curcuma longa L. (Zingiberaceae)	Compound (ar-) turmerone at serial concentrations of 1.56 to 25 μg/mL	Compound induced proliferation of neural stem cells (NSC) from fetal rats. In vitro and in vivo, turmerone promoted the neuronal differentiation of NSC. In vivo, after intracerebroventricular (i.c.v.) injection of the compound, there was greater proliferation of NSC from the subventricular zone (SVZ) and hippocampus of adult rats. It is suggested (Ar-) turmerone as a promising candidate in the regeneration of neurological disease	Hucklenbroich *et al.*, 2014 Germany

Curcuma longa L. (Zingiberaceae)	Curcuminóides diarylalkyls curcumin (CCN), demethoxycurcumin (DMCCN) and bisdemetoxicurcumina (BDMCCN) extracted from rhizomes and tested at concentrations (200, 500, and 1000 μM)	The human β-amyloid enzyme (BACE-1) is a key enzyme responsible for the production of amyloid plaques, which implies the progress and symptoms of Alzheimer's diseas. Curcuminoids CCN, DMCCN and BDMCCN inhibited the activity of BACE-1 in the Drosophila model. Structural features, such as degrees of saturation, functional group and hydrophobicity, appear to be involved in the inhibitory action of curcuminoids against BACE-1	Wang *et al.*, 2014 Republic of Korea
Curcuma longa L. (Zingiberaceae)	Curcumin (10 μM)	Curcumin improved microglial viability against amyloid β (Aβ42) and suppressed the expression of Aβ42-induced CD68 glycoprotein. It decreased the levels of IL-1β and interleukin-6 (IL-6) and TNF-α induced by Aβ42. It exerted an inhibitory effect on the phosphorylation of the ERK1/2 MAPK and p38 MAPK pathways induced by Aβ42 in the microglia, thus attenuating the inflammatory responses of the cerebral microglia	Shi *et al.*, 2015 China
Curcuma longa L. (Zingiberaceae)	Pretreatment with curcumin (2,5–20 μmol/L) for 24 h	Curcumin supressed induced apoptosis through the overexpression of appoptosin in cells of dopaminergic neurons SH-SY5Y (human neuroblastoma). It induced a positive regulation of HO-1 expression, reducing the production of intracellular heme and ROS, preventing loss of mitochondrial membrane potential (ΔΨm)	Zheng *et al.*, 2015 China
Curcuma longa L. (Zingiberaceae)	Curcumin intragastrically administered (100 mg/kg) twice a day for 50 days	Curcumin attenuated oxidative damage such as rotenone-induced dopaminergic neuronal loss in the central nervous system (SNpc) of rats through the activation of the Akt / Nrf2 signaling pathway. Curcumin relieved motor dysfunction, increased GSH levels, and reduced ROS activity and malondialdehyde (MDA) content. Increase suppressed tyrosine hydroxylase (TH) activity in the SNpc of rotenone (ROT)‑injured rats. Treatment with the compound restored levels of HO-1 and expression of NADPH	Cui *et al.*, 2016 China
Curcuma longa L. (Zingiberaceae)	Ethanolic extract	KCHO-1 is a product composed of 30% of ethanolic extracts obtained from the leaves of nine plants, including C. Longa. Preparation showed direct neuroprotective effects on mouse hippocampal cells (HT22). KCHO-1 suppressed levels of cellular damage and generation of ROS induced by glutamate and H2O2. KCHO-1 increased the mRNA and protein expression levels of HO-1, induced the extracellular activation of ERK and increased nuclear translocation of Nrf2	Lee *et al.*, 2016 Republic of Korea
Curcuma longa L. (Zingiberaceae)	Curcumin at a dose of 200 mg/kg/day or 300 mg/kg/day via gavage for 2 weeks	Compound protects neuronal cells against status epilepticus-induced hippocampal neuronal damage in the lithium-pilocarpine-induced status epilepticus in rat model through induction of autophagy and inhibition of necroptosis. Results have demonstrated an alteration in expression of Beclin-1 and Microtubule-associated protein	Wang *et al.*, 2016 China

		1A/1B-light chain 3 (LC3) proteins for autophagy and mixed lineage kinase domain-like (MLKL) protein and protein kinase-1 (RIP-1) for necroptosis in almost all four regions (CA1, CA3, DG, and H) of rat hippocampus	
Glycine max (L.) Merr. (Fabaceae)	Compound soyasaponin I (5, 10, and 20 mg·kg-1) was administered orally once a day for 4 weeks	Oral administration of soyasaponin I exhibited significant memory-enhancing effects in the passive avoidance, Y-maze, and Morris water maze tests in rats. Oral administration of soyasaponin I increased the amount of neural precursor cells (NPCs), cell proliferation markers (Ki-67), and neuronal differentiation (NeuN, TUJ1, and MAP2). The compound also increased neurite prolongation and the number of neurites during the differentiation of NPCs. Soyasaponin I can enhance learning and protect memory impairment by promoting the proliferation and differentiation of NPCs in the hippocampus by facilitating neuronal regeneration and minimizing neuroinflammation	Hong *et al.*, 2013 Republic of Korea
Matricaria chamomilla L. (Asteraceae)	Hydroalcoholic extract leaves (25 mg·kg-^{1}, i.p.)	Administration of extract before formalin injection showed decrease of pain responses in both phases of formalin test and showed has anti inflammatory effects in the second phase of formalin. Injection of extract and cisplatin together have shown that extract is able to decrease the second phase of cisplatin-induced pain. Extract have analgesic and painful neuropathic effects, is able to decrease cisplatin-induced pain and inflammation better than morphine.	Abad *et al.*, 2011 Iran
Matricaria chamomilla L. (Asteraceae)	Compound Apigetrin (12.5, 25, 50, or 100 μM) for 24 h	Compound reduced mRNA expression and secretion of inflammatory cytokines, TNF-α and IL-6, prostaglandin E2 (PGE2) level, suppressed expression of NF-kB, all stimulated by lipopolysaccharide (LPS), besides nitric oxide (NO) production, as well as expression of COX-2 and iNOS in BV-2 mouse micróglia. Apigetrin enhanced expression of antioxidant enzymes, HO-1 and Nrf2 in BV-2 cells. Compound also increased 2,20-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity, indicating antioxidative activity. Finaly, apigetrin inhibited H2O2-induced cell death in HT22 hippocampal cells	Lim *et al.*, 2016 Republic of Korea
Mentha piperita L. (Lamiaceae)	Aqueous extract from leaves was administered to rats by oral gavages at a dose of 1 g/kg body weight/day for seven consecutive days	Extract activity reduced gamma radiation-induced neuronal injury in rats. The biochemical analysis registered a decrease in GR and SOD levels after treatment with extract. Several histopathological changes were detected in rat brain tissues, such as pyrolysis signals in pyramidal cells of the cortex, nuclear vacuolization, apoptosis and neural degeneration. In the rats irradiated with gamma rays pretreated with the extract, there was an improvement in all the parameters tested above by means of a state of homeostasis and stabilization of the DNA cycle with a clear improvement in the analysis of the cell cycle	Hassan *et al.*, 2013 Egypt

		and in the defense system antioxidant	
Mikania laevigata Sch.Bip. ex Baker (Asteraceae)	Ethanolic extract leaves (40 µl/mL)	Pretreatment of extract for 30 min before incubation with *Philodryas olfersii* venom (50 µg/mL) completely protected mouse phrenic nerve-diaphragm (PND) from neuromuscular blockade and delayed the blockade in chick biventer cervicis (BC). Pretreatment of the preparations with extract protected against venom-induced muscle damage by 80.3% and 60.4% in PND and BC, respectively, and prevented TNF-α and interferon gamma (IFNγ) expression. The extract protected nerve-muscle preparations against the myotoxic, neurotoxic and inflammatory effects of *P. olfersii* venom	Collaço *et al.*, 2012 Brazil
Momordica charantia L. (Cucurbitaceae)	Lyophilized fruit juice (6.5 g powder/100 g of fresh juice). The powder so obtained was oral administrated in diabetic mice (200-800 mg/kg, p.o., o.d.)	The cerebral oxidative stress and damage, and neurological deficits were dose dependently attenuated. Moreover, pre-treatment with the lyophilized juice also exhibited dose dependent antihyperglycemic activity in diabetic mice	Malik *et al.*, 2011 India
Passiflora incarnata L., (Passifloraceae)	Formulations of ethanolic extract from leaves (fresh leaves: 65% EtOH and aqueous, dried leaves: 65% EtOH at 4° C, EtOH 65% at 100° C and aqueous) continuous administration in the drinking water (1000 mg freeze dried extract/kg/day; equivalent to between 4.2 and 13 g of dry herb/kg/day depending on preparation method) for one week	Whole Passiflora extract induced prominent, dose-dependent direct $GABA_A$ receptor currents in hippocampal slices. Aqueous extracts of fresh leaves and dried leaves 65% EtOH at 4° C exhibited anticonvulsant effects against pentylenetetrazole (PTZ) -induced convulsions in CF-1 mice. Anxiogenic effects in the elevated plus maze were seen in mice receiving any of the five *Passiflora* extracts in vitro assays	Elsas *et al.*, 2010 USA
Passiflora incarnata L., (Passifloraceae)	Hydroethanolic extract leaves (150, 300, and 600 mg/kg; i.p.)	Extract suppressed PTZ-induced seizures and improved post-ictal depression associated. The treatment reduced the severity of epileptic seizures in a dose-dependent manner and also attenuated serotonin and noradrenaline levels in the brain, With better action than the antiepileptic drug diazepam	Singh *et al.*, 2012 India
Passiflora incarnata L., (Passifloraceae)	Ethanol extract from leaves (30, 100 and 300 mg/kg body weight (bw)) for 7 weeks	Oral extract administration reduced memory anxiety rates in rats. Extract administration influenced the reduction of the content of glutamic acid and cortical serotonin in the hippocampus. The results partially confirmed the proposed mechanism of action of *P. incarnata* involving GABA receptors, which is the main inhibitory neurotransmitter in the brain	Jawna-Zboińska *et al.*, 2016 Poland
Punica granatum L. (Lythraceae)	Pomegranate peel methanolic extract (200 mg/kg bwt)	Extract attenuated neurotoxicity by decreasing aluminum chloride-induced oxidative stress in in brain of female rats, and these effects may be related to the stimulation of anti-	Abdel Moneim, 2012 Spain

		apoptotic protein (Bcl-2) and antioxidant activities	
Punica granatum L. (Lythraceae)	*P. granatum* peel methanolic extract (75 and 150 mg of kg body weight) administred for 45 days	Administration of the extract decreased the oxidative stress in the brain of diabetic mice induced by aloxane, regulating the antioxidant defense mechanism, attenuating the lipid and protein oxidation. Supplementation with the extract showed increased SOD and GPX activity and decreased MDA, with the most evident changes in the hippocampus region	Middha *et al.*, 2012 India
Punica granatum L. (Lythraceae)	Extract of fruits from pomegranate (225 mg/kg) for seven days once a day through orogastric gavage	Extract treatment exhibited neuroprotective effects in rats by attenuating oxidative stress and inflammatory response in the sciatic nerve, increasing total antioxidant capacity and decreasing levels of TNF-α, IL-1β and MDA	Celik *et al.*, 2013 Turkey
Punica granatum L. (Lythraceae)	Fruit Seeds Essential Oil (2,0 mg/mL)	Neuroprotective effect of the essential oil reversed cytotoxicity in neuronal cells (PC12) induced by 3-nitropropionic acid- (3-NP), which may be due to the ability of the oil to neutralize ROS, NO, LPx and LDH generated by neurotoxicity Induced by 3-NP (100 mM), increasing levels of antioxidant enzymes	Al-Sabahi *et al.*, 2014 India
Punica granatum L. (Lythraceae)	Pomegranate seed oil (PSO) was unlimitedly administered; and ater-soluble nanoemulsions from PSO (Nano-PSO) administered either by gavage 5 times a week (150 µl/day),	Nano-PSO delayed the development of Alzheimer's disease when given in mice TgMHu2ME199K (exhibit typical pathological features of human CJD, Creutzfeldt Jacob disease, and of general neurodegeneration) and postponed the worsening of the disease in already sick animals. Analysis of brain samples revealed that the treatment reduced lipid oxidation and neuronal loss, indicating a neuroprotective effect	Mizrahi *et al.*, 2014 Israel
Punica granatum L. (Lythraceae)	Juice of the pomegranate fruits (6.5–7.5 mL of fluid per day) administered in their drinking water for two weeks	Pomegranate juice exhibited neuroprotective effects in a rat model of rotenone that induces Parkinson's Disease. Oral administration juice of the pomegranate fruits did not mitigate or prevent experimental Parkinson's disease, but instead increased nigrostriatal terminal depletion, DA neuron loss, the inflammatory response and caspase activation, thereby heightening neurodegeneration. Observed increased nitrotyrosine levels, inducible nitric oxide synthase, and activated caspase-3 expression in nigral DA neurons is consistent with potential pro-oxidant activity of Pomegranate juice	Tapias *et al.*, 2014 USA
Ruta graveolens L. (Rutaceae)	Aqueous extract of leaves (0,01, 0,1, 1 and 10 mg/mL) for 24, 48 and 72 hours	Extract induced cell death in glioblastoma lines (U87MG, C6 and U138), through the activation of the pathways by ERK1/2 and AKT. Interestingly, the rutin compound, isolated from the aqueous extract, does not induce cell death, suggesting that rutin alone is not responsible for the neuroprotective effects	Gentile *et al.*, 2015 Italy
Zingiber officinale Roscoe (Zingiberaceae)	Compound 6-shogaol (1, 5 and 10 µM) and doses of 5 mg/kg and 20 mg/kg once per day for 3 days in model in mice	6-shogaol suppressed the activation of LPS-induced microglia in neuronal-glia cortical primary culture and showed neuroprotective effects in an in vivo neuroinflammatory model, acting on transient global ischemia through inhibition of microglia. It has been shown	Ha *et al.*, 2012 Republic of Korea

		to be an effective therapeutic agent for the treatment of neurodegenerative diseases by inhibiting the production of PGE2, IL-1β, TNF-α, p38 MAPK and NF-κB	
Zingiber officinale Roscoe (Zingiberaceae)	Aqueous extract of the rhizomes (0.1 mL/kg bw) was injected into the Baihui point for a period of 14 days after the occlusion of MCAO	Extract co-administered to pharmacopuncture improves cognitive function and decreases oxidative stress after cerebral ischemia induced by occlusion of the MCAO in mice. Animals submitted to ginger treatment with pharmacopuncture presented increased levels of CAT and GPX, both cerebral cortex and hippocampus	Jittiwat & Wattanathorn, 2012 Thailand
Zingiber officinale Roscoe (Zingiberaceae)	Aqueous extract of the rhizomes	Extract showed protective properties against Fe^{2+}-induced lipid peroxidation in rat brain homogenates in vitro. The extract caused a significant decrease in the MDA contents of the brain of mice in a dose-dependent manner. The oxidative stress in the brain could be potentially managed/prevented by dietary intake of ginger	Oboh *et al.*, 2012a Nigeria
Zingiber officinale Roscoe (Zingiberaceae)	Aqueous extract of ginger rhizomes (100 μL)	Extract exerted anti-Alzheimer properties in the rat brain in in vitro models. The extract inhibited the activity of AchE, sodium nitroprusside (SNP) and quinoline (QA) induced by lipid peroxidation, which can be attributed to the presence of phytochemicals such as flavonoids, alkaloids, tannins and terpenoids	Oboh *et al.*, 2012b Nigeria
Zingiber officinale Roscoe (Zingiberaceae)	Fresh ginger ethanolic extract (0.125–0.5 mg/mL) and compounds 8-gingerol, 10-gingerol, 6-shogaol (5–20 μM) for 20 h of treatment	Compounds inhibited the production of nitric oxide, IL-1β, IL-6 and TNF-α as well as their mRNA levels in LPS-activated BV2 microglia. Blocking NF-κB activation was the underlying mechanism responsible for inhibiting the proinflammatory gene expression. Fresh ginger extract exhibited a significant anti-neuroinflammatory capacity, which was largely owing to 10-gingerol	Ho *et al.*, 2013 Taiwan
Zingiber officinale Roscoe (Zingiberaceae)	Hydro-alcoholic extract of fresh ginger rhizome (200 or 300 mg/kg bw, every other day) for 30 days by i.p. injection	Extract modulated the expression of IL-27 (is expressed by a variety of immune and non-immune cells, such as T cells, monocytes, dendritic cells, mast cells, hepatocytes, endothelial cells, neurons, B cells and NK cells) (up-regulated) and IL-33 (reported that IL-33 levels were elevated in the periphery and of the central nervous system of multiple sclerosis patients, implicating that IL-33 may participate in the pathogenesis of multiple sclerosis) (down-regulated) in the spinal cord of mice in an experimental autoimmune encephalomyelitis (EAE) model	Jafarzadeh *et al.*, 2014 Iran
Zingiber officinale Roscoe (Zingiberaceae)	Capsulets of powder of ginger rhizome (250 mg) only one capsulet upon headache onset	Capsule administered in a randomized, double-blind clinical trial with 100 patients who had acute migraine was shown to be effective in the treatment of migraine attacks, with effect comparable to the drug sumatriptan. Capsule administration had a lower incidence of side effects than the drug	Maghbooli *et al.*, 2014 Iran
Zingiber officinale Roscoe (Zingiberaceae)	Compound 6-gingerol (25 μM) trated for 24 h	6-gingerol induced cell death of meningioma (IOMM-Lee and CH157MN cells) by apoptosis with phosphorylation of glycogen synthase kinase 3β (GSK3β) and inhibition of the Wnt5/β-catenin pathway. Apoptosis may be associated to	Das *et al.*, 2015 USA

		downregulation of tetraspanin protein (TSPAN12), survival proteins (Bcl-XL and Mcl-1), and overexpression apoptotic factors (Bax and caspase-3)	

From the selected articles in the two databases (Figure Nº 2), more than a third of the publications occurred in 2012 (34.92%). *Curcuma longa* L. (turmeric) was the medicinal plant with the highest number of published data totalizing 30 studies (47,62% of all selected articles).

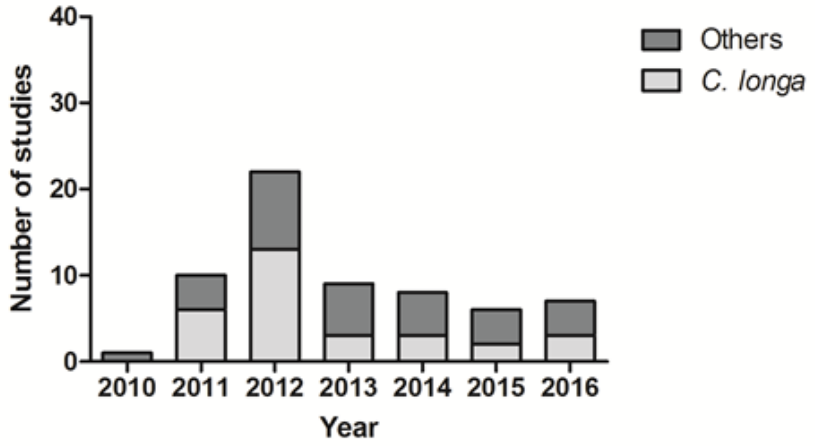

Figure Nº 2
Number of publications with neuroprotective potential distributed between 2010 and 2016, between RENISUS and C. Longa plants, plant with the largest amount of research.

Out of the 63 articles, only three studies were developed by Brazilian institutions (Jaques *et al.*, 2012; Zanotto-Filho *et al.*, 2012; Collaço *et al.*, 2012). We would have expected an increase in Brazilian scientific research after the creation of RENISUS, although that was not the case here. In terms of the 71 medicinal herbs of RENISUS, only 12 plant species were reported within the scope of our review. Out of 12 plants with neuroprotective potential, two species, *Glycine max* L. (soy) and *Mentha piperita* L. (pepper mint), is currently available at SUS as phytotherapy. In addition, *Mikania laevigata* Sch.Bip. ex Baker (guaco) and *Passiflora incarnata* L. (passion fruit) are representative Brazilian plants.

It is worthy to highlight that this systematic review evaluated so only a period of scientific production after the creation of RENISUS. Nevertheless, it is noteworthy that before and after that period numerous plant species have been scientifically proven for their neuroprotective potential including *Panax ginseng* C.A. Mey. (Chinese ginseng) (Van Kampen *et al.*, 2014), *Ginkgo biloba* L. (ginkgo) (Saleem *et al.*, 2008), *Salvia officinalis* L. (sage) (Eidi *et al.*, 2006), *Hypericum perforatum* L. (St John's wort) (Silva *et al.*, 2004), *Morus alba* (white mulberry) (Kang *et al.*, 2006) and *Bacopa monnieri* L. (Brahmi) (Calabrese *et al.*, 2008).

DISCUSSION

The present systematic review identified 63 reports on the effects of 12 medicinal herbs listed in RENISUS on neuroprotective potential. Neuroprotective properties are defined here as the ability to counteract and attenuate mechanisms that

may contribute to the pathogenesis and progression of neurodegenerative disorders. The pooled data revealed that the identification and characterization of new phytochemicals extracted from medicinal plants are vital for the development of new drugs for the treatment of neurological diseases such as the neurodegenerative ones. The potential of plants is justified by their importance in the most different medical applications. In addition, several plants traditionally used that were not the object of our study may also offer a great field for research to proving the efficacy and safety of their administration (Bolson *et al.*, 2015; Adebayo *et al.*, 2015).

One of the most active compounds studied was curcumin, which is a polyphenol antioxidant of low molecular weight. It was first extracted from *C. longa* rhizomes thousands of years ago by Asians (Srivastava *et al.*, 1985). Curcumin is one of the active phytochemicals found in high concentration in species of Zingiberaceae family and it has an exceptional safety profile and a number of pleiotropic actions with potential neuroprotective efficacy that can be achieved at submicromolar level (Chin *et al.*, 2013). All these facts corroborate with the number of studies on turmeric and ginger found in this review.

As demographics move towards an aging population, neurological pathologies become one of the main challenges to the modern health care system. Therefore, the zeal directed by public health agencies for the use of medicinal plants has increased substantially. Since 1978, the World Health Organization (WHO) has been funding significant public investment in projects related to medicinal plants. Consequently, an increase in public interest in natural therapies can be seen in developing and developed countries resulting in growing acceptance of herbal medicines by health professionals and the population in general (Calvo & Cavero, 2015).

Despite the abundance of Brazilian flora, the therapeutic profile of innumerous plants has not been properly explored (Oliveira *et al.*, 2013; Martins *et al.*, 2016). Seeking to enhance the knowledge of existing natural products in the country, since 2012, Brazil's Ministry of Health launches funds focused on projects and research on medicinal plants. Since the creation of the fund, 66 projects in the country were awarded with budgets that totalize US$ 7 million (Brazil, 2015). In this context, in order to guide and encourage professionals to prescribe plants and herbal medicines, ANVISA published in June 2016, the Herbal Memento, which gathers detailed information on numerous RENISUS plants, containing data on contraindications, precautions for use, adverse effects, drug interactions, routes of administration and dosage (Brazil, 2016).

CONCLUSION

In conclusion, the outcomes of this systematic review have disclosed the neuroprotective potential of 12 selected plant species of RENISUS. Data from preclinical studies showed that medicinal herbs might have potential benefit for the management of neurodegenerative diseases. In addition, the above-mentioned beneficial properties of RENISUS plants contribute substantially to the medicinal knowledge of potentially important species, and this review can be used as a guide to new researches in the neurological field.

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